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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/019,501	OGATA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-10,12-22,25,26 and 28* is/are pending in the application.

4a) Of the above claim(s) *12-15 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-10,16,18-22,25,26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/16/06 has been entered.

2. Claims 4-10, 12-22, 25-26 and 28 are pending.

3. Upon reconsideration, claims 16 and 18-22 have been rejoined with the elected group.

4. Claims 12-15 and 17 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

5. Claims 4-10, 16, 18-22, 25-26 and 28, drawn to a method of maintaining or increasing low vasopressin level, a method of treating at least one symptom caused by a decrease in vasopressin level and a method of inhibiting the binding between PTHrP and a receptor thereof comprising administering to the patient at least one anti-PTHrP antibody or binding fragment thereof, are being acted upon in this Office Action.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 4, 16, 18-20 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of maintaining or increasing low vasopressin level comprising administering to a patient at least one antibody or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 or a monoclonal antibody produced by the hybridoma deposited as FERM BP-5631 or a humanized #23-57-137-1 antibody wherein the antibody or binding fragment thereof inhibits the binding of PTHrP to its receptor as set forth in claims 5-10, 21, 25-26 and 28, **does**

not reasonably provide enablement for (1) a method of maintaining or increasing low vasopressin level comprising administering to a patient any one or more modified antibody or antigen binding fragment thereof that binds specifically to SEQ ID NO: 75 wherein the modification is any "amino acid substitution" or any "chemical modification" as set forth in claim 4, and (2) a method of inhibiting the binding between PTHrP and a receptor thereof comprising providing any "substance", any substance such as any anti-PTHrP antibody, any fragment of any anti-PTHrP antibody, any modified form of any fragment, any humanized anti-PTHrP antibody, any chimeric anti-PTHrP antibody, and any monoclonal antibody as set forth in claims 16, 18-20 and 22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses a method maintaining or increasing low vasopressin level by administering to a patient a monoclonal or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75, see page 23-23, Figure 1. The monoclonal antibody #23-57-137-1 that binds specifically to N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 is produced by hybridoma deposited as FERM BP-5631. The deposit has been made under the terms of the Budapest Treaty on August 15, 1996 at the National Institute of Bioscience and Human-technology Agency of Industrial Science and Technology, Japan (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan) under the accession No. FERM BP-5631 as indicated at page 24. A declaration by Masao Haruna filed October 20, 2004, who is associated with the patent owner, stating that the hybridoma FERM BP-5631 secreting the antibody #23-57-137-1 has been deposited under the Budapest Treaty and that said hybridoma FERM BP-5631 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent had satisfied the deposit requirement made herein. The specification further discloses a method of making chimeric or humanized #23-57-137-1 thereof

that binds specifically to human PTHrP 1-34 consisting of the amino acid sequence of SEQ ID NO: 75 for inhibits the binding of PTHrP to its receptor and thereby ameliorates the low blood vasopressin levels associated with cancer such as mice implanted with human large cell lung carcinoma LC-6, which is a human hypercalcemia model (see Figure 1). The specification discloses anti-PTHrP antibody can be conjugated to e.g., polyethylene glycol; PEG), see page 13 at last line. The specification also discloses the specific amino acid substitutions in the light chain of monoclonal antibody #23-57-137-1 such as the ones disclosed at page 62 for making humanized antibody.

However, the specification does not teach how to make any modified antibody (claim 4) having any amino acid substitution or any chemical modification such that the modified antibody still binds specifically to SEQ ID NO: 75 for the claimed method. There is insufficient guidance and in vivo working example as to which amino acids within the full-length sequence of immunoglobulin heavy and light chains of which anti-PTHrP antibody or binding fragment thereof to be substituted such that the modified antibody or binding fragment still binds specifically to SEQ ID NO: 75, let alone which amino acid substitution *maintaining* low vasopressin levels and/or which amino acid substitutions *increasing* low vasopressin level for the claimed methods.

The state of the prior art as exemplified by Abaza *et al*, of record, is such that even a single amino acid substitution outside the antigenic site can exert drastic effects on the binding specificity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the unlimited number of amino acid substitution, it is unpredictable which antibody modification is associated with maintaining low vasopressin and which modification is associated with increasing low vasopressin level. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to chemically modified anti-PTHrP antibody that binds specifically to SEQ ID NO: 75, the specification discloses conjugating antibody to polyethylene glycol; PEG), see page 13 at last line. The specification does not teach any chemically modified antibody.

The state of the prior art as exemplified by Banerjiee et al (J Immunology 169: 5137-5144, 2002; PTO 892) is such that chemical modification such as reduction and alkylation affect the conformation of the protein-antibody interaction. Banerjiee et al teach disrupting interchain disulfide bonds between cysteine in close proximity on the protein surface and antigen binding

region of antibody such as IgE by reducing agent such as DTT resulted in complete loss of IgE antibody binding to protein (see abstract, page 5141, col. 2, first paragraph, in particular).

With respect to a method of inhibiting the binding between PTHrP and a receptor thereof comprising providing any "substance" (claim 16) and "modified form of the fragment" (claim 19), there is insufficient guidance as to the structure of such "substance" and "modified form of the fragment" without the chemical structure and/or amino acid sequence, let alone how to make and use such undisclosed "substance" and "modified form of the fragment" for inhibiting the binding between any PTHrP and any receptor thereof. Further, the "modified form of the fragment" does not even have to come from the antibody.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Given the unlimited number of "substance" and "modified form of any fragment" and without guidance as to the structure and in vivo working example, an undue amount of experimentation would be required to determine how to practice the claimed invention.

Even assuming the modified form of the fragment is an anti-PTHrP antibody fragment (claim 19), is it an antigen binding fragment or the Fc fragment? Further, there is insufficient guidance as to which amino acids within the fragment of any anti-PTHrP to be substituted, deleted, added and/or a combination thereof such that the fragment still binds specifically to PTHrP of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor(s).

Even if the substance is limited to an anti-PTHrP antibody (claim 18), humanized or chimeric anti-PTHrP antibody (claim 20), and monoclonal antibody (claim 22) and antigen binding fragment thereof for the claimed method, the specification does not teach any antibody and fragment mentioned above bind to *any* PTHrP, especially any other part of any PTHrP such as C-terminal part of any and all PTHrP that is effective for inhibiting binding between PTHrP and a receptor thereof.

The specification discloses only monoclonal antibody, humanized antibody, chimeric antibody and antigen binding fragment thereof that binds specifically to *human* PTHrP N-

terminal residues (1-34) consisting of the amino acid sequence of SEQ ID NO: 75 wherein the antibody and antigen binding fragment thereof inhibits the binding of PTHrP to its receptor. This is because antibody to other part of PTHrP such as the C-terminus of PTHrP does not bind to its receptor; antibody that binds to the C-terminus of PTHrP and blocking PTHrP from binding to its PTHrP receptor has yet to be demonstrated. It has been well known to those skilled in the art at the time the invention was made that minor structural differences in the antigen would change the binding specificity of the antibody.

Kuby *et al*, of record, teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in antibody specificity that differs from the antibody specificity directed against the native full-length polypeptide. Given the unlimited number of PTHrP and PTHrP antibody, there is insufficient guidance and in vivo working example showing that any antigen such as any PTHrP would produce antibody that binds specifically to human PTHrP, let alone any anti-PTHrP such as any humanized PTHrP, chimeric PTHrP and monoclonal antibody would inhibit the binding between any PTHrP and any of its receptor for the claimed method.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 11/16/06 have been fully considered but are not found persuasive.

Applicants' position is that claims 1, 11, 23, 24, and 27 have been canceled, thus rendering the rejections of these claims moot. As currently amended, claims 4, 5, 7, 8, and 25 depend from allowed claim 26, thus incorporating all of the allowed limitations of claim 26. Furthermore, claim 9 has been amended to incorporate the allowable limitations from claim 26 of

"at least one anti-PTHrP antibody, or binding fragment thereof' and "wherein the antibody, or binding fragment thereof, binds specifically to SEQ ID NO: 75." As currently amended, claim 4 recites, "a modified antibody.., wherein said modification is selected from amino acid substitution and chemical modification." In one embodiment of amended claim 4, the antibody is modified by "amino acid substitution." Reference Example 4 (Specification pages 47-67) teaches methods for making antibodies modified by amino acid substitution. Nineteen modified antibodies are disclosed, encompassing 50 amino acid substitutions. Reference Example 4 also teaches the determination of antigen-binding ability for the modified antibodies and Reference Example 5 (Specification pages 67-69) teaches the determination of neutralizing activity for the modified antibodies. For example, the specification states, "it was found that, among the humanized antibodies having the same levels of antigen-binding activity as that of the chimeric antibody, those antibodies having L-chain versions... (in which the 91-position tyrosine was replaced by isoleucine) exhibited the similar neutralizing activity to that of the chimeric antibody." (Specification page 68.)

In response, the argument with respected to canceled claims 1, 11, 23, 24, and 27 is moot since said claims have been canceled.

Although claim 4 has been amended, amended claim 4 still encompasses any modified antibody having any "amino acid substitution" or any "chemical modification".

The specification discloses anti-PTHrP antibody can be conjugated to e.g., polyethylene glycol; PEG), see page 13 at last line. The specification also discloses the specific amino acid substitutions in the light chain of monoclonal antibody #23-57-137-1 such as the ones disclosed at page 62 for making humanized antibody.

However, the specification does not teach how to make any modified antibody (claim 4) having any amino acid substitution or any chemical modification such that the modified antibody still binds specifically to SEQ ID NO: 75 for the claimed method. There is insufficient guidance and in vivo working example as to which amino acids within the full-length sequence of immunoglobulin heavy and light chains of which anti-PTHrP antibody or binding fragment thereof to be substituted such that the modified antibody or binding fragment still binds specifically to SEQ ID NO: 75, let alone which amino acid substitution *maintaining* low vasopressin levels and/or which amino acid substitutions *increasing* low vasopressin level for the claimed methods.

The state of the prior art as exemplified by Abaza *et al*, of record, is such that even a single amino acid substitution outside the antigenic site can exert drastic effects on the binding specificity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the unlimited number of amino acid substitution, it is unpredictable which antibody modification is associated with maintaining low vasopressin and which modification is associated with increasing low vasopressin level. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

With respect to chemically modified anti-PTHrP antibody that binds specifically to SEQ ID NO: 75, the specification discloses conjugating antibody to polyethylene glycol; PEG), see page 13 at last line. The specification does not teach any chemically modified antibody.

The state of the prior art as exemplified by Banerjiee et al (J Immunology 169: 5137-5144, 2002; PTO 892) is such that chemical modification such as reduction and alkylation affect the conformation of the protein-antibody interaction. Banerjiee et al teach disrupting interchain disulfide bonds between cysteine in close proximity on the protein surface and antigen binding region of antibody such as IgE by reducing agent such as DTT resulted in complete loss of IgE antibody binding to the protein (see abstract, page 5141, col. 2, first paragraph, in particular). Given the unlimited number of chemical modification, it is unpredictable which antibody modification is associated with maintaining low vasopressin and which modification is associated with increasing low vasopressin level. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention.

8. Claims 4, 16, 18-20, 22 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** for (1) any "modified antibody" that binds to SEQ ID NO: 75 wherein the modification is any "amino acid substitution", any "chemical modification", or any chemical modification is thyroglobulin conjugation for the method of *maintaining* low vasopressin level in a subject for the claimed method, (2) any "modified antibody" that binds to SEQ ID NO: 75 wherein the modification is any "amino acid substitution", any "chemical modification" or any chemical modification is

thyroglobulin conjugation for the method of *increasing* low vasopressin level in a subject, (3) any "substance" that inhibits the binding between any PTHrP and its receptor, (4) any substance is any anti-PTHrP antibody that inhibits the binding between any PTHrP and its receptor, (5) any substance is any "modified form of the fragment" that inhibits the binding between any PTHrP and its receptor, (6) any humanized anti-PTHrP antibody, (7) any anti-PTHrP chimeric antibody and (8) any monoclonal anti-PTHrP antibody that inhibits the binding between any PTHrP and its receptor thereof for the claimed method of inhibiting the binding between any PTHrP and a receptor thereof.

The specification discloses a method maintaining or increasing low vasopressin level by administering to a patient a monoclonal or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75, see page 23-23, Figure 1. The monoclonal antibody #23-57-137-1 that binds specifically to N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 is produced by hybridoma deposited as FERM BP-5631. The deposit has been made under the terms of the Budapest Treaty on August 15, 1996 at the National Institute of Bioscience and Human-technology Agency of Industrial Science and Technology, Japan (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan) under the accession No. FERM BP-5631 as indicated at page 24. A declaration by Masao Haruna filed October 20, 2004, who is associated with the patent owner, stating that the hybridoma FERM BP-5631 secreting the antibody #23-57-137-1 has been deposited under the Budapest Treaty and that the hybridoma FERM BP-5631 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent has satisfied the deposit requirement made herein. The specification further discloses a method of making chimeric or humanized #23-57-137-1 thereof that binds specifically to human PTHrP 1-34 consisting of the amino acid sequence of SEQ ID NO: 75 for inhibits the binding of PTHrP to its receptor and thereby ameliorates the low blood vasopressin levels associated with cancer such as mice implanted with human large cell lung carcinoma LC-6, which is a human hypercalcemia model (see Figure 1). The specification discloses anti-PTHrP antibody can be conjugated to e.g., polyethylene glycol; PEG), see page 13 at last line. The specification also discloses the specific amino acid substitutions in the light chain of monoclonal antibody #23-57-137-1 such as the ones disclosed at page 62 for making humanized antibody.

With the exception of the methods mentioned above using the specific anti-human $PTHrP_{1-34}$ antibody mentioned above that binds to SEQ ID NO: 75, there is insufficient written description about any "modified" anti-PTHrP antibody that binds specifically to SEQ IDNO: 75

having any one or more "amino acid substitution" within the immunoglobulin heavy and light chains of which antibody that binds specifically to SEQ ID NO: 75 to be substituted for which amino acids, let alone which amino acid substitution(s) maintaining low vasopressin levels and which amino acid substitution(s) increasing low vasopressin levels for the claimed method.

With regard to any chemically modified anti-PTHrP antibody for the claimed method, the claim encompasses any chemical modified antibody. The specification discloses only polyethylene glycol (PEG) conjugated antibody that binds to SEQ ID NO: 75. Other than the disclosed PEG conjugated antibody, the other chemically modified antibody for the claimed method is not adequately described.

With regard to any chemically modified anti-PTHrP antibody that binds to SEQ ID NO: 75 wherein the chemically modification is thyroglobulin conjugation in the method of claim 28, the recitation of the method wherein the antibody is modified by thyroglobulin conjugation in newly added claim 28 represents a departure from the specification and the claims as originally filed. The passage pointed out by applicant in the amendment filed 11/26/06 does not provide a clear support for *anti-PTHrP antibody* conjugated to *thyroglobulin*. The specification at page 23 lines 14-15 discloses the *immunogen* (PTHrP1-34) was conjugated to a carrier protein thyroglobulin, NOT the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 conjugated to thyroglobulin as now claim. **This is new matter**.

With respect to a method of inhibiting the binding between PTHrP and a receptor thereof comprising providing any "substance" (claim 16) and any "modified form of the fragment" (claim 19), there is inadequate written description about the structure associated with function of any "substance", and any "modified form of the fragment" without the amino acid sequence. Let alone such undisclosed substance and modified form of any fragment inhibits the binding of any and all PTHrP to any and all receptors thereof. Further, the "modified form of the fragment" in claim 19 does not even have to come from the anti-PTHrP antibody. Even assuming the modified form of the fragment is from anti-PTHrP, it is not clear if the antibody fragment is the antigen binding fragment or the Fc fragment and if so, which amino acids within such fragment to be modified by substitution, deletion, addition and/or combination such that it still binds specifically to any PTHrP, any PTHrP such as human PTHrP of SEQ ID NO: 75, in turn, inhibits the binding of which PTHrP and its receptor. As such, any substance is any fragment of any anti-PTHrP antibody and any substance is any "modified form of any fragment" for the claimed method are not adequately described.

With respect to the substance is an anti-PTHrP antibody (claim 18) for the method of inhibiting between PTHrP and a receptor thereof, the specification discloses only antibody that binds specifically to the N-terminus residues 1-34 of human PTHrP consisting of the amino acid sequence of SEQ ID NO: 75 for the claimed method. The specification discloses the N-terminus of human PTHrP binds to its receptor and antibody to the N-terminus residues 1-34 of human PTHrP inhibits the binding between human PTHrP and its receptor. The specification does not disclose antibody such as any monoclonal, any humanized, any chimeric antibody, any human antibody any binding fragment thereof that binds to any and all PTHrP. The specification does not disclose antibody such as any monoclonal, any humanized, any chimeric antibody, any human antibody and any binding fragment thereof that binds to any part of any PTHrP such as the C-terminus of human PTHrP is effective for inhibiting the binding between PTHrP and a receptor thereof. Even assuming the fragment is an antibody fragment, not all fragment of an antibody such as Fc fragment of an anti-PTHrP antibody binds to PTHrP, let alone inhibits the binding between any PTHrP and receptor thereof. Further, even assuming the fragment is a modified antibody fragment, there is inadequately written description about which amino acids within the antibody fragment to be substituted, deleted, added and/or combination thereof such that the modified form of the fragment, presumably an antibody fragment, still binds specifically to human PTHrP of SEQ ID NO: 75, in turn, would be useful for inhibiting the binding between PTHrP and its receptor.

Other than N-terminal of human PTHrP1-34 of SEQ ID NO: 75 to which the antibody binds for the claimed methods, the binding specificity of any substance, any modified form of any fragment, any anti-PTHrP antibody, any modified form of any anti-PTHrP antibody fragment for the claimed method is not adequately described.

The specification discloses only antibody that binds to *human* PTHrP consisting of the amino acid sequence of SEQ ID NO: 75, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of substance, modified form of the fragment, anti-PTHrP antibody, and modified fragment thereof to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 11/16/06 have been fully considered but are not found persuasive.

Applicants' position is that as currently amended, claim 4 recites, "a modified antibody.., wherein said modification is selected from amino acid substitution and chemical modification." In one embodiment of amended claim 4, the antibody is modified by "amino acid substitution." Reference Example 4 (Specification pages 47-67) teaches methods for making antibodies modified by amino acid substitution. Nineteen modified antibodies are disclosed, encompassing 50 amino acid substitutions. Reference Example 4 also teaches the determination of antigen-binding ability for the modified antibodies and Reference Example 5 (Specification pages 67-69) teaches the determination of neutralizing activity for the modified antibodies. Thus, contrary to the Office's arguments, the specification provides ample guidance "as to which amino acids within the binding region of the antibody fragment (CDRs) to be modified." (Office Action pages 7 and 9.) For example, the specification states, "it was found that, among the humanized antibodies having the same levels of antigen-binding activity as that of the chimeric antibody, those antibodies having L-chain versions... (in which the 91-position tyrosine was replaced by isoleucine) exhibited the similar neutralizing activity to that of the chimeric antibody." (Specification page 68.) In another embodiment of amended claim 4, the antibody is modified by "chemical modification." Reference Example 1 (Specification pages 23-24) teaches methods for producing chemically conjugated modified antibodies. Specifically, this example teaches the preparation of an anti-PTHrP (1-34) antibody conjugated with a thyroglobulin carrier protein using carbodiimide (Dojinn). The specification also teaches that "[t]he modified antibodies can be prepared by chemical modifications of the antibodies" and that "[t]he chemical modification techniques suitable for this purpose have already been established in the art." (Specification page 14.)

In response, amended claim 4 still encompasses any modified antibody having any "amino acid substitution" or any "chemical modification".

The specification discloses a method maintaining or increasing low vasopressin level by administering to a patient a monoclonal or antigen binding fragment thereof that binds specifically to the N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75, see page 23-23, Figure 1. The monoclonal antibody #23-57-137-1 that binds specifically to N-terminal 1-34 of human PTHrP consisting of SEQ ID NO: 75 is produced by hybridoma deposited as FERM BP-5631. The deposit has been made under the terms of the Budapest Treaty on August 15, 1996

at the National Institute of Bioscience and Human-technology Agency of Industrial Science and Technology, Japan (1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan) under the accession No. FERM BP-5631 as indicated at page 24. A declaration by Masao Haruna filed October 20, 2004, who is associated with the patent owner, stating that the hybridoma FERM BP-5631 secreting the antibody #23-57-137-1 has been deposited under the Budapest Treaty and that the hybridoma FERM BP-5631 will be irrevocably and without restriction or condition released to the public upon the issuance of a patent has satisfied the deposit requirement made herein. The specification further discloses a method of making chimeric or humanized #23-57-137-1 thereof that binds specifically to human PTHrP 1-34 consisting of the amino acid sequence of SEQ ID NO: 75 for inhibits the binding of PTHrP to its receptor and thereby ameliorates the low blood vasopressin levels associated with cancer such as mice implanted with human large cell lung carcinoma LC-6, which is a human hypercalcemia model (see Figure 1). The specification discloses anti-PTHrP antibody can be conjugated to e.g., polyethylene glycol; PEG), see page 13 at last line. The specification also discloses the specific amino acid substitutions in the light chain of monoclonal antibody #23-57-137-1 such as the ones disclosed at page 62 for making humanized antibody.

With the exception of the methods mentioned above using the specific anti-human $PTHrP_{1-34}$ antibody mentioned above that binds to SEQ ID NO: 75, there is insufficient written description about any "modified" anti-PTHrP antibody that binds specifically to SEQ IDNO: 75 having any one or more "amino acid substitution" within the immunoglobulin heavy and light chains of which antibody that binds specifically to SEQ ID NO: 75 to be substituted for which amino acids, let alone which amino acid substitution(s) maintaining low vasopressin levels and which amino acid substitution(s) increasing low vasopressin levels for the claimed method.

With regard to any chemically modified anti-PTHrP antibody for the claimed method, the claim encompasses any chemical modified antibody. The specification discloses only polyethylene glycol (PEG) conjugated antibody that binds to SEQ ID NO: 75. Other than the disclosed PEG conjugated antibody, the other chemically modified antibody for the claimed method is not adequately described.

With regard to any chemically modified anti-PTHrP antibody that binds to SEQ ID NO: 75 wherein the chemically modification is thyroglobulin conjugation in the method of claim 28, the recitation of the method wherein the antibody is modified by thyroglobulin conjugation in newly added claim 28 represents a departure from the specification and the claims as originally filed. The passage pointed out by applicant in the amendment filed 11/26/06 does not provide a

clear support for *anti-PTHrP antibody* conjugated to *thyroglobulin*. The specification at page 23 lines 14-15 discloses the *immunogen* (PTHrP1-34) was conjugated to a carrier protein thyroglobulin, NOT the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 conjugated to thyroglobulin as now claim. **This is new matter.**

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 16 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamamoto et al (of record, Endocrinology 138(5): 2066-2072, 1997; PTO 1449).

Yamamoto et al teach a method of inhibiting the binding between PTHrP such as PTHrP1-34 and its receptor such as Type I PTHrP receptor in the rat supraoptic nucleus (SON) by providing a substance such as PTHrP(7-34) and allowing the PTHrP(7-34) to inhibit the binding between PTHrP1-34 and Type I PTHrP receptor (see abstract, page 2068, col. 2, Binding of 125I-labeled [Tyr34] to crude membranes isolated from rat SON, in particular). The reference PTHrP(7-34) is a fragment of PTHrP and modified by conjugating to 125I label at the Tyr34 residue. Thus, the reference teachings anticipate the claimed invention.

12. Claims 4-10, 16, 18, 20-22 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,903,194 B1 (of record, filed September 24, 1997; PTO 892).

The '194 patent teaches a method of treating a symptom as a results of cancer such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules that leads to hyperuresis (polyuria), anorexia and nausea dehydration due to insufficient uptake of water which are all associated with low vasopressin levels (see col. 1, lines 42-61, in particular). The reference method inhibits the binding of PTHrP to its receptor by administering to a patient an anti-PTHrP antibody such as a monoclonal antibody, humanized antibody, chimeric antibody and/or human antibody thereof that binds to human PTHrP 1-34, wherein the reference human PTHrP 1-34 is 100% identical to the claimed SEQ ID NO: 75 (see entire document, claim 11 of the '194 patent, col. 7, lines 41-57, reference SEQ ID NO: 75, col. 3, lines 64-65, col. 14, lines 56, claims 1-6 of the '194 patent, col. 10, lines 60-67, col. 30, lines 50, col. 24, lines 10, in particular). The reference monoclonal antibody #23-57-1371 is produced by hybridoma deposited under accession No. FERM BP-5631 (see col. 27, lines 29-36, in particular). The '194 patent also teaches modification of the reference antibody by amino acid substitution at the specific position in the light chain such as replacing glycine amino acid at position 43 for proline and replacing the 49-positon lysine amino acid at position 49 for aspartic acid (see col. 46, lines 63 bridging col. 47, lines 1-2, in particular). The '194 patent also teaches humanized antibody #23-57-1371 antibody which is identical to the humanized #23-57-137-1 in the claimed method (see col. 24, line 15, in particular).

Given the reference method uses the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as maintaining low vasopressin level as claimed (see col. 2, lines 42-52, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

13. Claims 4-10, 16, 18, 20-22 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by CA 2,266,332 publication (published April 2, 1998; PTO 892).

The CA 2,266,332 patent teaches a method of treating at least one symptom caused by a decrease in vasopressin levels as a results from cancer such as polyuria and dehydration (see page 2, lines 7-24, page 135, in particular) by administering to patient such as animal or human (see page 49, lines 1-14, in particular) at least one anti-PTHrP such as monoclonal antibody, chimeric or humanized antibody (see page 14, page 55, page 76, in particular) and/or human antibody thereof (see claim 46 of the CA 2,266,332 patent, in particular) that binds specifically to human PTHrP1-34 of SEQ ID NO: 75, which is which is 100% identical to the claimed SEQ ID NO: 75 (see paragraph bridging pages 14-15, in particular). The CA 2,266,332 patent teaches monoclonal antibody #23-57-1371 produced by deposited hybridoma FERM BP-5631 (see page 55, line 4, in particular) and humanized antibody #23-57-1371 (see page 49, page 103, and pages 118, 121, in particular). The CA 2,266,332 patent also teaches modification of the reference antibody by amino acid substitution at the specific position in the immunoglobulin light chain such as replacing glycine amino acid at position 43 for proline and replacing the 49-positon lysine amino acid at position 49 for aspartic acid (see Table 3 at page 103, paragraph bridging page 97 and 98, in particular). The CA 2,266,332 patent also teaches humanized antibody #23-57-1371 antibody which is identical to the claimed humanized #23-57-137-1.

Given the reference method uses the same antibody to treat the same patient population via the same mechanism where the antibody binds to human PTPrP1-34 of SEQ ID NO: 75 and inhibits the binding between PTHrP and its receptor, the reference method inherently has the same effect such as maintaining low vasopressin level as claimed (see page 2 of CA266,332, lines 7-24, in particular). Further, as defined in the instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Thus, the reference teachings anticipate the claimed invention.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 4, 9-10, 16, 19, 25-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,903,194 B1 (of record, filed September 24, 1997; PTO 892) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of the '194 patent have been discussed supra. The '194 patent teaches the antibody that binds to PTHrP is useful for treating the symptoms associated with humoral hypercalcemia of malignancy with higher therapeutic effects and less side-effects upon consecutive used (see col. 2, lines 42-57, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 9 differs from the teachings of the reference only in that the method of treating at least one symptom caused by a decrease in vasopressin level comprising administering to the patient a modified form of the anti-PTHrP antibody fragment instead of a whole antibody.

The invention in claim 19 differs from the teachings of the reference only in that the method of inhibiting the binding between PTHrP and a receptor thereof wherein the substance is a fragment of an anti-PTHrP.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 28 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified by polyethylene glycol (PEG) conjugation.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, F(ab')2 antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody such as conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) or whole antibody (see page 1393, first paragraph, in particular). The advantages of PEG conjugated antibody or antibody binding fragment thereof are that PEG reduces the immunogenicity of any monoclonal antibody as well as extending the half life of the antibody, especially the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to make antibody fragment such as $F(ab')_2$ and then chemically modify the antibody $F(ab')_2$ fragment or any antibody by conjugating the antibody fragment or antibody to polyethylene glycol as taught by Kitamura et al using the whole monoclonal antibody, humanized antibody, chimeric antibody or human antibody that binds specifically to PTHrP of SEQ ID NO: 75 for a method of maintaining low or increasing vasopressin level by inhibiting the binding of PTHrP to its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically

modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The '194 patent teaches antibody such as monoclonal, humanized, chimeric or human antibody that binds to PTHrP of SEQ ID NO: 75 is useful for treating the symptoms associated with malignancy such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules leas to hyperuresis (polyuria), and anorexia and nausea accompanied with dehydration which all resulted from low levels of vasopressin levels (see col. 2, lines 42-57, in particular).

17. Claims 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,903,194 (of record, filed March 25, 1999: PTO 892) in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of the '194 patent have been discussed supra.

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, scFv or Fv instead of whole antibody that binds specifically to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent using the monoclonal, human antibody, chimeric or humanized

PTHrP antibody that binds specifically to SEQ ID NO: 75 for a method of maintaining low vasopressin by inhibiting the binding between human PTHrP and its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The '194 patent teaches the PTHrP antibody is useful for treating at least one symptom such as hypercalcemia, polyuria, or dehydration, that caused by cancer (see col. 1, lines 42-61, in particular) which resulted in inherent low vasopressin levels (see col. 60, line 6-18, in particular).

18. Claims 4, 9-10, 16, 19, 25-26 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over CA 2,266,332 patent (published April 2, 1998; PTO 892) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of CA 2,266,332 patent have been discussed supra. The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP of SEQ ID NO: 75 is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side-effects upon consecutive used (see page 14, page 133, and page 135, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 9 differs from the teachings of the reference only in that the method of treating at least one symptom caused by a decrease in vasopressin level comprising

administering to the patient a binding fragment of an anti-PTHrP antibody instead of a whole antibody.

The invention in claim 19 differs from the teachings of the reference only in that the method of inhibiting the binding between PTHrP and a receptor thereof wherein the substance is a fragment of an anti-PTHrP.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 28 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified by polyethylene glycol (PEG) conjugation.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, F(ab')2 antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody such as conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) or whole antibody (see page 1393, first paragraph, in particular). The advantages of PEG conjugated antibody or antibody binding fragment thereof are that PEG reduces the immunogenicity of any monoclonal antibody as well as extending the half life of the antibody, especially the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to make antibody fragment such as $F(ab')_2$ and then chemically modify the antibody $F(ab')_2$ fragment or any antibody by conjugating the antibody fragment or antibody to polyethylene glycol as taught by Kitamura et al using the whole monoclonal antibody, humanized antibody, chimeric antibody or human antibody that binds

specifically to PTHrP of SEQ ID NO: 75 for a method of maintaining low vasopressin level by inhibiting the binding of PTHrP to its receptor as taught by the CA 2,266,332 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular).

19. Claims 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over CA 2,266,332 patent (published April 2, 1998; PTO 892) in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of CA 2,266,332 patent have been discussed supra. The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular).

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, scFv or Fv instead of whole antibody that binds to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and

internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent using any antibody such as monoclonal, human antibody, chimeric or humanized antibody that binds specifically to SEQ ID NO: 75 for a method of maintaining low vasopressin by inhibiting the binding between human PTHrP and its receptor as taught by the CA 2,266,332 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The CA 2,266,332 patent teaches the reference humanized antibody or human antibody to human PTHrP is less immunogenic and useful in treating the symptoms associated with humoral hypercalcemia associated with malignancy with higher therapeutic effects and less side effects upon consecutive used (see page 14, page 133, and page 135, in particular).

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

21. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

22. Claims 4-10, 16, 18, 20-22 and 26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. US Pat No 6,903,194 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issuance of a patent to instant claims which drawn to a method of inhibiting the binding between PTHrP and its receptor by administering a genus of substance such as monoclonal antibody, humanized antibody, chimeric antibody, human antibody or binding fragment thereof that binds to human PTHrP (1-34) of SEQ ID NO: 75 as well as monoclonal antibody produced by the hybridoma deposited as FERM BP-5631, wherein the low vasopressin levels as resulted from malignant cancer would include the method of inhibiting the binding between PTHrP and a receptor thereof in claim 11 of the '194 patent comprising administering the humanized antibody that binds specifically to human PTHrP1-34 of the issued patent (species) wherein the humanized antibody is an agent for suppressing hypercalcemia or hypophosphatema associated with malignant tumor.

Further, given the method of the '194 patent teaches the same antibody to treat the same patient population, the method of the '194 patent inherently has the same effects such as

maintaining or increasing low vasopressin level wherein the low levels of vasopressin is associated with cancer. As defined in instant specification, "a decrease in vasopressin level may result from any cause, preferably from cancer or cancer-induced hypercalcemia of malignancy and examples of symptoms caused by a decrease in vasopressin level include, but are not limited to polyuria, dehydration, and mouth dryness" (see specification at page 17, lines 2-8). Claim 4 is included in this rejection because the '194 patent also teaches modified antibody by amino acid substitution such as version b of the humanized antibody (see col. 46, lines 63 bridging col. 47, lines 1-2, in particular). Claim 6 is included in this rejection because the '194 patent also teaches antibody produced by the same deposited hybridoma FERM BP-5631 (see col. 27, lines 29-36, in particular).

23. Claims 4, 9-10, 16, 19, 25-26 and 28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. 6,903,194 B1 (of record) in view of Kitamura et al (of record, Biochemical and Biophysical Research Communication 171(3): 1387-1394, 1990; PTO 892).

The teachings of the '194 patent have been discussed supra. The '194 patent teaches the antibody that binds to PTHrP is useful for treating the symptoms associated with humoral hypercalcemia of malignancy with higher therapeutic effects and less side-effects upon consecutive used (see col. 2, lines 42-57, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified.

The invention in claim 9 differs from the teachings of the reference only in that the method of treating at least one symptom caused by a decrease in vasopressin level comprising administering to the patient a binding fragment of an anti-PTHrP antibody instead of a whole antibody.

The invention in claim 19 differs from the teachings of the reference only in that the method of inhibiting the binding between PTHrP and a receptor thereof wherein the substance is a modified form the fragment of an anti-PTHrP.

The invention in claim 25 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is $F(ab')_2$ fragment instead whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 26 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the antibody is binding a fragment instead of whole anti-PTHrP antibody that binds specifically to SEQ ID NO: 75.

The invention in claim 28 differs from the teachings of the reference only in that the method of maintaining low vasopressin level wherein the anti-PTHrP antibody that binds specifically to SEQ ID NO: 75 is chemically modified by polyethylene glycol (PEG) conjugation.

Kitamura et al teach antibody fragment such as $F(ab')_2$ fragment and is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor in vivo such as high tumor:blood ratio (see page 1388, page 1392, in particular). However, F(ab')2 antibody has a faster plasma clearance from blood compared with whole IgG (see page 1390, Blood circulation, in particular). Kitamura et al teach chemically modified antibody such as conjugating polyethylene glycol (PEG) to antibody fragment $F(ab')_2$ (see page 1391, in particular) or whole antibody (see page 1393, first paragraph, in particular). The advantages of PEG conjugated antibody or antibody binding fragment thereof are that PEG reduces the immunogenicity of any monoclonal antibody as well as extending the half life of the antibody, especially the antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). Further, PEG modification increases the uptakes of F(ab')2 fragment in both tumor and blood compared to PEG-modified whole antibody monoclonal antibody (see page 1393, 3rd paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as $F(ab')_2$ and then chemically modify the antibody $F(ab')_2$ fragment or any antibody by conjugating the antibody fragment or antibody to polyethylene glycol as taught by Kitamura et al using the whole monoclonal antibody, humanized antibody, chimeric antibody or human antibody that bind specifically to PTHrP of SEQ ID NO: 75 for a method of maintaining or increasing low vasopressin level by inhibiting the binding of PTHrP to its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Kitamura et al teach antibody fragment such as $F(ab')_2$ is useful for tumor targeting since it retains binding specificity of the parent antibody, and accumulates in tumor at a higher ratio (see page 1388, page 1392, in particular). Kitamura et al further teach the advantages of chemically

modified antibody such as PEG conjugated antibody or PEG conjugated antibody binding fragment are that PEG reduces the immunogenicity of the mouse monoclonal antibody and it also extends the half life of the antibody or antibody fragment in circulation (see paragraph bridging pages 1392 and 1393, in particular). The '194 patent teaches antibody such as monoclonal, humanized, chimeric or human antibody that binds to PTHrP of SEQ ID NO: 75 is useful for treating the symptoms associated with malignancy such as hypercalcemia, reduction of water concentrating ability due to lesion of the renal distal tubules leas to hyperuresis (polyuria), and anorexia and nausea accompanied with dehydration which all resulted from low levels of vasopressin levels (see col. 2, lines 42-57, in particular).

24. Claims 25-26 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 11 of U.S. Patent No. 6,903,194 B1 in view of Harlow *et al* (of record, in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory patent, Cold Spring Harbor, NY, pages 626-629) or US Pat No. 4,946,778 (of record, Aug 1990, PTO 892).

The teachings of the '194 patent have been discussed supra.

The claimed invention in claim 25 differs from the teachings of the reference only in that the method wherein the antibody is Fab, scFv or Fv instead of whole antibody that binds specifically to SEQ ID NO: 75.

Harlow et al teach a method of producing antibody fragment from any antibody such as Fab fragment or $F(ab')_2$ (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody such as scFv or Fv (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make antibody fragment such as Fab as taught by Harlow et al or scFv or Fv as taught by the '778 patent using the monoclonal, human antibody, chimeric or humanized

PTHrP antibody that binds specifically to SEQ ID NO: 75 for a method of maintaining low vasopressin by inhibiting the binding between human PTHrP and its receptor as taught by the '194 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

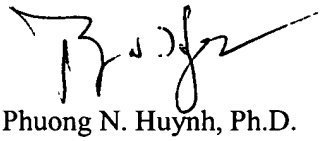
One having ordinary skill in the art would have been motivated with an expectation of success to do this because Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). The '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application as taught by the '788 patent (See column 3, lines 33-48, in particular). The '194 patent teaches the PTHrP antibody is useful for treating at least one symptom such as hypercalcemia, polyuria, or dehydration, that caused by cancer (see col. 1, lines 42-61, in particular) which resulted in inherent low vasopressin levels (see col. 60, line 6-18, in particular).

25. No claim is allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

27. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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